REMARKS

Claims 1, 4, 8, 10, 12, 16-19, 22, 24, 27 and 35 remain pending in the application. Applicants request cancellation claims 2, 3, 5-7, 9, 11, 13-15, 20-21, 23, 25-26, 28-34 and 36-48, without prejudice or disclaimer, for being drawn to non-elected subject matter. Applicants reserve the right to prosecute these claims in successive divisional or continuation applications. No new matter has been added.

Rejection under 35 U.S.C. § 102/§ 103

Claims 1, 4, 8, 10, 12, 16-18, 35 and 49 have been rejected under 35 U.S.C. § 102(b) as being anticipated, or in the alternative, obvious under 35 U.S.C. § 103 in view of Lezdey *et al.* (U.S. Patent No. 5,532,215) ("Lezdey"). Applicants traverse.

The Examiner alleges that Lezdey "teaches that conjugates of heparin and serpins which have active sites can be used in the method of inhibiting HIV proliferation." (Page 3, third paragraph of the Office Action). The Examiner also notes that "Lezdey teaches a method for inhibiting HIV proliferation by inhibiting viral replication of killing the viruses on contact via human serine protease inhibitors such as antithrombin..." (Page 3, third paragraph of the Office Action). Applicants disagree.

Independent claims 1, 8, and 35 all specify that the antithrombin must be selected from the group consisting of 43 kDa modified antithrombin, R-antithrombin, S-antithrombin, pre-latent antithrombin, a variant thereof, an analog thereof and a combination thereof. Likewise, claim 45 specifies that the antithrombin must be antithrombin III. Lezdey does not teach or suggest any of these specific molecules. For a reference to anticipate a claim, it must teach every limitation of that claim. Since Lezdey does not teach the molecules specified in the claims, it cannot anticipate them. Likewise, as there is also no suggestion of these molecules in Lezdey these claims are also not obvious in view of this reference.

In the rejection of claim 49, the Examiner also alleges, that the term antithrombin is "synonymous" with the term antithrombin III. (*See* page 3, first paragraph of the Office Action). Applicants respectfully disagree. Webster's Revised Unabridged Dictionary defines "synonymous" as follows. "Having the character of a synonym; expressing the same thing; conveying the same, or approximately the same, idea." The terms antithrombin and antithrombin III do not express the same thing or convey the same or approximately the same idea.

As defined by a search of the GenBank database, "antithrombin" refers to a 57 amino acid protein having accession number BAC21173. "Antithrombin III" is defined in the GenBank database as a 464 amino acid protein with accession number AAB40025. (The GenBank entries for these accession numbers are included as Exhibit A). Therefore, Applicants contend that the terms antithrombin and antithrombin III neither express the same thing nor convey the same or approximately the same idea. Thus, since Lezdey cannot teach or suggest antithrombin III, it does not anticipate claim 49, or render it obvious.

Further, the term "antithrombin" is also not synonymous with "43 kDa modified antithrombin", "R-antithrombin", "S-antithrombin", or "pre-latent antithrombin". 43 kDa modified antithrombin (mATIII) is purified CD8+ T-cell antithrombin III ("ATIII"). Native, unmodified ATIII has a molecular weight of 54-65 kDa, whereas mATIII has a molecular weight of 43 kDa. (*See* page 15, lines 10-12 of the instant specification). Moreover, as indicated on page 12, lines 20-22 of the instant specification, R-antithrombin, ("R-ATIII") is antithrombin III cleaved between serine 386 and threonine 387. S-antithrombin ("S-ATIII") is the stressed comformation of antithrombin III as when it is bound to heparin. (*See* page 12, lines 12-15 of the instant specification). Pre-latent antithrombin ("pre-latent ATIII") is S-ATIII incubated for 24 hours at 60 °C under physiological salt conditions. Thus, Applicants contend that none of these subtypes of antithrombin III are synonymous with the terms "antithrombin III" or with the term "antithrombin". Therefore, as Lezdey does not teach or suggest every limitation of claims 1, 8 and 35, it does not anticipate these claims or render them obvious.

Likewise, claims 4, 10, 12, and 16-18 each depend from one of these independent claims. As such, they necessarily include all of the limitations of these claims. Therefore, for the reasons set forth above, Applicants contend that these claims are also not anticipated or obvious in view of Lezdey.

The Examiner also alleges that, because Lezdey (Column 3, lines 16-19) states that heparin, along with PVA and PEG, may be useful in the methods disclosed in Lezdey and that Lezdey teaches S-antithrombin. Moreover, the Examiner also alleges that Lezdey teaches serpins (such as antithrombin) that bind to heparin. Applicants disagree. First, Applicants note that S-antithrombin is the conformation that antithrombin III assumes when it binds to heparin. As explained above, antithrombin III is not disclosed in Lezdey. Second, Applicants note that heparin is only mentioned in Lezdey in the context of the subject matter of Mitra (U.S. Patent

No. 4,496,689) ("Mitra") (Included as Exhibit B). Mitra describes a process of conjugating alpha-1-proteinase inhibitor to heparin, as well as to other water soluble polymers such as PVA and PEG. (*See* Mitra at claims 1-3). The use of heparin as disclosed in Lezdey is for the conjugation of serpins to a water soluble polymer for administration to a patient. The use of heparin is not a specific teaching or suggestion of S-antithrombin as an effective antiviral composition.

The Examiner further alleges that Lezdey teaches that antithrombin can be used to inhibit the proliferation of HIV and directs Applicants' attention to column 5, lines 17-25; column 6, line 31; and column 3, lines 39-41 as evidence supporting this contention.

Applicants note that the relevant portions of Lezdey, cited by the Examiner, do not teach or suggest that antithrombin inhibits HIV proliferation. The text of Lezdey at column 5, lines 17-25 mentions serpins but not antithrombin. Column 6, lines 17-25, describes the properties of alpha-2-macroglobulin, which is not a serpin. (*See* Lezdey column 3, line 42). Moreover, column 3, lines 39-41, taken from the Background section of Lezdey, teaches that antithrombin is a serpin. This is the only reference to antithrombin in Lezdey. Thus, while Lezdey does disclose that antithrombin is a serpin, it teaches that serpins other than antithrombin are preferred, or even functional, in the treatment of HIV. All of the experimental evidence provided in Lezdey regarding the use of serpins, refers to alpha-1-antitrypsin and alpha-1-antichymotrypsin. Thus, based on the teaching of Lezdey, Applicant contends that one of ordinary skill in the art would not know whether antithrombin would be functional as an antiviral treatment, as there is no teaching or suggestion in Lezdey regarding the use of antithrombin in the treatment of HIV and there is no experimental evidence to this effect.

The Examiner further alleges that claims 16-18, drawn to amounts of antithrombin to be administered, are anticipated or obvious in view of Lezdey because, "one of ordinary skill in the art would know how to administer the antithrombin, as evidenced by Lezdey which teaches sample dosages of serpin alpha-2-macroglobulin." (*See* page 3, second paragraph of the Office Action). As noted above, Lezdey states that alpha-2-macroglobulin is not a serpin. (*See* column 3, line 42 of Lezdey). Also, the dosage suggested by Lezdey for the alpha-2-macroglobulin (*e.g.* 60 mg/kg of body weight) is different from those recited in claims 16-18.

Thus, Applicants contend that one of ordinary skill in the art would not have a reasonable expectation of success of dosing the specific antithrombin III proteins of the invention based on

the information regarding one sample dose of an unrelated protein, that is provided by Lezdey. Lezdey does not teach or suggest the dosages or the specific proteins described in claims 16-18. Therefore, claims 16-18 are not anticipated by or obvious in view of Lezdey.

Based on the above arguments, Applicants contend that claims 1, 4, 8, 10, 12, 16-18, 35, and 49 are not anticipated by or obvious in view of Lezdey. Therefore, Applicants request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 19, 22, 24, and 27 have been rejected under 35 U.S.C. § 103 for being obvious over Lezdey, in view of Hopkins (WO96/10639) ("Hopkins"). According to the Examiner, "Hopkins teaches modified serine protease inhibitors, including antithrombin . . . One would have had a reasonable expectation of success that Hopkins' method of gene delivery and expression would work in the method of Lezdey. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." Applicants traverse.

As explained above, Lezdey does not teach the use of the specific antithrombins recited in the instant claims in order to inhibit HIV infection. Applicants contend that one of ordinary skill in the art would not have had a reasonable expectation of success using the antithrombin III disclosed in Hopkins in the methods disclosed in Lezdey. As discussed above, there is nothing in Ledzey to indicate that the specific antithrombins claimed herein could be used to treat HIV infection.Thus, Applicants contend that the Examiner has failed to set forth a proper *prima facie* case of obviousness. Therefore, Applicants request that this rejection of these claims be withdrawn.

CONCLUSION

Applicants submit that the claims as here amended put the application in condition for allowance, and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is invited and encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

for Reg No 48223

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Customer No. 30623

Dated: May 11, 2004

TRA 1907645v3



☐ 1: BAC21173. antithrombin [Hom...[gi:23978630] BLink, Links

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REFERENCE   1
  AUTHORS   Kinoshita,S., Iida,H., Inoue,S., Watanabe,K., Kurihara,M., Wada,Y.,
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  TITLE     Gene Analysis of Anticoagulation Factors in Japanese Thrombotic
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REFERENCE   2  (residues 1 to 57)
  AUTHORS   Hamasaki,N.
  TITLE     Direct Submission
  JOURNAL   Submitted (14-APR-2002) Naotaka Hamasaki, Kyushu University
            Hospital, Department of clinical chemistry and laboratory medicine;
            3-1-1 maidashi, Higashi-ku Fukuokasi, Fukuoka 812-8582, Japan
            (E-mail:hamasaki@cclm.med.kyushu-u.ac.jp, Tel:81-92-642-5770,
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☐ 1: AAB40025. antithrombin III ...[gi:179130] BLink, Domains, Links

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